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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/618,083	07/14/2003	Ping Huang	034536-0318	3626

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EXAMINER	
PATEL, SUDHAKER B	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/618,083	HUANG ET AL.	
	Examiner	Art Unit	
	Sudhaker B. Patel, D.Sc.Tech.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7,9-11,14-17,19-30,32,34,35,37-41 and 43-48* is/are pending in the application.

4a) Of the above claim(s) *6,8,12,13,18,31,33,36,42 and 49-89* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,9,14,15,22-30,32,34,35,40,41 and 45-48* is/are rejected.

7)☒ Claim(s) *10,11,16,17,19-21,37-39,43 and 44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/28/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' communication paper sated 7/28/04 is acknowledged.

Election/Restrictions

Because applicants did not distinctly and specifically point out the supposed errors in the restriction/election requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Applicant's election without traverse of invention of Group II, and also election of species of Example 36 as recited in Figure 1, has following meanings of the variables in generic Formula (II).

R1	: Zero;
Q	: CF3SO2-;
B	:substituted heteroaryl;
A2	:A Bond with zero atom in length;
R2	: (CO) OR wherein R= H;
(n)	: 1.

Preliminary search did not revel any art for the species of Example 36. Therefore, search was expanded to the invention of Group II.

Since the claims 1-5,7,9,10,11,14,15,16,17,19-30,32,34,35,37-41,43-48 link with other inventions, they will be examined bearing in mind the subject matter and species as elected by the applicants and restriction as stated above. Claims 6, 8, 12, 13, 18, 31, 33, 36, 42 are withdrawn from further consideration as they represent non elected subject matter, and there being no allowable generic or linking claim 37CFR 1.142(b). Election was made without traverse in paper dated 7/28/04.

Restriction/election is considered proper and is now made FINAL.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 7/14/04 is being considered by the examiner. Signed copy of PTO Form 1449 is enclosed with this communication for applicants' record.

Claim Objections

2. Claims 10,11,16,17,19,20,21,37,38,39,43,44 are objected to because of the following informalities: These claims include subject matter that is either already patented or consist of non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. Claims 1,16-20,21,39,48, 21,23,24 and claims dependent on these claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. The claims1, 16,21,39,48 recite B variables:" phenyl as well as aryl". What is included or excluded in recitation of " aryl ". Correction is required.

5. The claims 1,16,21,39,48 recite B variable as:" heteroaryl, heterocyclic ring(s)". Claims do not recite is exactly and definitely the compounds and chemical structures included in such a generic definition. Rings actually made and as tested in the specification are required.
6. Claims 16-20 related to pharmaceutical composition recite the composition consisting of either a compound of generic Formulae or its pharmaceutically acceptable salt or solvate". Usually an inert carrier is also present in such composition(s). Correction is required.
7. Claim 21, which is related to a method of treating a disorder, does not exactly and definitely recite a specific single disorder. Correction is required.
8. Claim 23 recites diabetes. A specific disorder is required.
9. Claim 24 recites:" neurological diseases". The claims do not recite a single specific disorder. What is excluded from the claimed diseases? Correction is required.
10. Claims 21, 48 are independent generic claims related to method of treating, regulating, inhibiting or modulating a protein tyrosine phosphatase signal transduction in a cell". The claims remain silent about the specific disease /disorder, and at the same time they do not mention about the exact step or process of administration.
11. Claim 48 does not recite:" to whom to be administered". Correction is required.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims21-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a single and definite disorder, does not reasonably provide enablement for regulat9ing, inhibiting or modulating protein tyrosine phosphatase signal transduction in a generic cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The method of use claims recite generic terms cancer, a solid tumor, epidermoid cancer, diabetes, neurological degenerative diseases, and disorders yet to be discovered.
14. In cases directed to chemical compounds, which are being used for their physiological/biological activity, the scope of the claims must have a reasonable correlation to the scope of enablement provided by the specification. See in re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group and In re Wiggins 179 USPQ 421.
15. "Compounds or pharmaceutically acceptable salts, and composition(s) thereof as recited in the claims read on all such moieties regardless of complexity of structure and point of attachment to the aliphatic or carboxylic or aromatic or heterocyclic core or bridge/chain for which there is no sufficient teaching how to make and how to use at any one selective location among the many possible sites present. The situation is more

confusing when a skilled person in the art tries to visualize the multiple possibilities of combining a claimed compound and/ or its pharmaceutical composition for treating a cell or a mammal having diseases or conditions associated with a generic, cancer, a solid tumor, diabetes, osteoporosis, neurodegeneratrive diseases, and diseases yet to be discovered in general. Applicants provide no reasonable assurance that any and all derivatives of the instant compounds and their compositions as outlined, will have ability to generate the compounds in vivo or in vitro by one or more processes.

16. In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ 2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include:*(1).* The nature of invention;*(2).* the state of prior art ;*(3).* the predictability or lack thereof in the art; *(4).* the amount of direction or guidance present;*(5).* the presence or absence of working examples;*(6).* the breadth of the claims, and *(7).* the quantity of experimentation needed.

1). The nature of the invention: The compounds and their method of use claim(s) are drawn in part to use them for treating a generic cell or a mammal which includes human beings, having diseases or conditions associated with cancer, tumor, osteoporosis, diabetes, neurodegenerative diseases, and diseases yet to be discovered in general.
2). The state of prior art: There are no known compounds of similar structure (i.e. compounds of invention that have been demonstrated for the treatment of a cell disorders/diseases as recited here in a generic way.

3). The predictability or lack thereof in the art: It is presumed in the use for patient(s) who are humans or animals suffering from disorder(s) or disease(s) related to activity of protein tyrosine phosphatase receptors as claimed herein, there is a way of identifying those cells or mammal(s) who may develop any kind of physiological conditions including (but not limited to) a single disease. There is no evidence of record, which would enable the skilled artisan in the identification of the patient(s) who have the potential of becoming afflicted with the physiological conditions related to cancer, tumor, osteoporosis, diabetes, neurodegenerative diseases, and diseases yet to be discovered in general.
4). The amount of direction or guidance present and 5).: The presence or absence of working examples: There are no doses, and patient-dosage regime present to direct one to treat a potential host from an infection or disease, and other multiples of physiologically related condition(s) of various types.

6). The breadth of the claims: The claims are drawn to physiological conditions (not limited to) for treatment associated with a cell, cancer, tumor, diabetes, neurodegenerative diseases, and diseases yet to be discovered in general, which are not related and whose treatment(s) is unknown by a single compound of instant invention.

7). The quantity of experimentation need would be and undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

17. ***Discussion about Tumors/cancer(s);***

For example, the claim sets forth not only for the treating tumor metastasis, but also for solid tumor growth and other diseases. However, there never has been a compound capable of treating various types of cancers. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancers and pain as recited earlier, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective anti-cancer agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologist today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task. This is only for one of the many disorders as claimed herein.

Following references are quoted to show the state of art for Tumor/cancer:

- ***Cecil Textbook of Medicine*** states that: " each specific type of cancer has unique biological and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body.
  Also see In re Butting, 163, USPQ 689 (CCPA 1969), wherein "evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers".
- ***Structure-Based Design of Novel Anticancer Agent:***

  Uckun et al(see Current Cancer Drug Targets, 1,59-71(2001) concludes in pages 66-67 that : " WHI-P131, which inhibits JAK3 but does not inhibit JAK1, JAK2, SYK,BTK,LYN or IRP even at concentrations as high as 350uM is undergoing further studies to evaluate its potential use as a new anti leukemic agent(in children). Agents that inhibit epidermal growth factor receptor(EGFR) may be useful for treatment of breast cancer. Tubulin modulating agents, which are of natural as well as synthetic origin, can be used as effective anticancer agents for treating breast cancer. COBRA compounds caused destruction of microtubule organization and apoptosis. Like other microtubule-interfering agents, COBRA

compounds activated the proapoptotic c-Jun N-terminal kinase (JNK) signal transduction pathway, as evidenced by rapid induction of c-jun expression".

18. Following references are cited to show the present state of art(s) for AD: Understanding about neurodegenerative disease/Alzheimer's disease:

■ Cecil's Textbook of Medicine, vol2, 20th Edn. (See pages1992-1996) for AD related Dementia, and in particularly Table 400-1 listing the most frequent causes of progressive dementia in page 1992.

■ Coyle et al(Science Vol.219, pages 1184-1190(1983)) cites in the summary that:" These cholinergic neurons provide widespread innervation of the cerebral cortex and related structures and appear to play an important role in cognitive functions, especially memory". The authors conclude (see page 1189) that:" The identification of a transmitter-specific pathway selectively affected in a major form of dementia is an important step in the design of diagnostic studies, investigations of pathogenic mechanisms, and the development of therapeutic approaches to these debilitating neuropsychiatric disorders".

18A. ***Following references are cited to show the present state of art(s) for p38,CSBP,RK:***

■ Lim et al(PubMed Abstract 9671412, also cited as Oncogene, 16/22,2915-26(1998)) state that:" induction of erg-1 gene growth factors and stress are mediated through different subgroups of MAP kinases which may also differently affect egr-1 function on its target genes".

■ ***Mechanism of activation of ERK, JNK/SAPK and P38/CSBP/RK, kinase family members:***

Liu et al(PubMed Abstract 8902523, also cited as Free Radic. Biol. Med. 21/6,771-81(1996))) state that:" Comparative studies with wild-type PC12 cells and PC 12 cells expressing a dominant negative Ras mutant allele indicated that arsenite activitates ERK primarily through a Ras-dependent pathway(s), while activities of both JNK/SAPK and p38 occurs through a mechanism relatively independent of Ras. These results suggest that JNK/SAPK and p38 may share common upstream regfulators distinct from those involved in ERK activation".

■ ***The role of cytokines in osteoarthritis pathophysiology:***

Fernandes et al (PubMed Abstract12082286, also cited as Biorheology, 39/1-2, 237-46(2002) state that:"Several studies illustrate the potential importance of modulating IL-1 activity as a means to reduce the progression of the structural changes in OA.... Future directions in the research and treatment of OA will be based on the emerging picture of pathophysiological events that modulate the initiation and progression of osteoarthritis".

19. Specification on pages 246-255 recites various test(s) and assay methods for binding activity of VLA-4 See pages 246-8. The results are summarized as:" Compounds havingf an IC50 of less than about 15 uM possess binding affinity to alpha4 beta 1. When tested in this assay, each of the compound prepared in the above

examples has or is expected to have an IC50 of 15 uM or less (or is expected to be active in vivo).

These results will only serve for the preliminary screening of many compounds, and not for treating the diseases in a mammal as claimed herein.

20. The facts as provided above do support the need for additional quantity of experimentation which would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the method of treatment for various disorders/conditions related to cancer, tumor, neurodegenerative disorders and other diseases.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of instant compounds to treat various disorders/diseases related to protein tyrosine phosphatase.

21. When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006.

Conclusion
Allowable Subject Matter

22. Claims1-5, 7,9,10,11,14,15 related to compounds and claims 16,17,19,20 related to compositions. would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph and other rejections/objections, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

23. Method of treatment claims if limited to a single and specific disease would also be considered for allowance, provided applicants submit additional data to support the claims.

24. The following is a statement of reasons for the indication of allowable subject matter: The closest prior art ref. Hunter et al (U.S.P. 4177057 dated 12/19979, also cited as Chemical Abstract DN 92:111017) teaches making of compounds having substituted benzimidazole core. The reference differs from the instant compounds by not having a –COOH group or a ring as claimed herein. The ref. 184 does not indicate or suggest to arriving at the instant invention.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sudhaker B. Patel, D.Sc.Tech. whose telephone number is (571) 272-0671.

The examiner can normally be reached on 6:30 to 5:00 pm (Monday-Thursday). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund J. Shah can be reached on (571) 272 0674 or Sr. Examiner Mr. Richard Raymond at (571) 272 0673 or Mr. James O. Wilson at (571) 272-0661.

The fax phone numbers for the organization where this application or proceeding is assigned are 703 308 4556 for regular communications and 703 308 4556 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308 1235.Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sudhaker B. Patel, D.Sc. Tech.
August 27, 2004.

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